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14. ABSTRACT Tibial stress fractures (TSFs) are a substantial problem in military training, but a means of predicting their occurrence remains elusive. Bone strength is key to the resistance of TSF, but bone density, a determinant of strength, is known not to predict TSF. Elasticity is nearly as important as density in determining bone strength but has not been tested in TSF, or even studied in runners. However, clinical studies of osteoporotic patients given bisphosphonates have shown significant correlations between low elasticity and fracture incidence. These basic validation studies will determine if modulators of tibial stress, such as strike mechanics and surface incline, also modulate bone elasticity during running. Because these modulators may operate on the tibia via muscles, we have combined ultrasound characterization of tibial elasticity with MRI monitoring of muscle recruitment during a running protocol in healthy volunteers.					
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Table of Contents

Cover.....	1
SF 298.....	2
Introduction.....	4
Body.....	4
Key Research Accomplishments.....	7
Reportable Outcomes.....	7
Conclusions.....	8
References.....	8
Appendices.....	none

Introduction

Tibial stress fractures (TSFs) are a substantial problem for military recruits, elite athletes, and adults transitioning from a sedentary lifestyle to an exercise regimen. Bone strength is key to the resistance of TSF, but it is evident that a better method of evaluating bone quality is needed, as the gold standard method (bone mineral densitometry) is known not to predict TSF risk. Furthermore, there is growing evidence that the influence of muscles on bone may be an important determinant of bone properties. This school of thought is embodied in Frost's Utah paradigm of skeletal physiology [1] where the load-bearing skeleton adapts to the voluntary mechanical loads induced by muscles. Ultrasound critical-angle reflectometry (UCR) is a novel modality developed in laboratory of Dr. Peter Antich that allows the complete anisotropic elastic properties of bone to be measured in vivo [2]. This modality does appear to show an association between low elasticity and fracture incidence in osteoporotic patients treated with bisphosphonate [3]. In this study, tibial stress will be modulated in subjects by varying running styles and treadmill inclination. Measuring changes in bone elasticity in relation to the muscle recruitment patterns as determined using magnetic resonance imaging (MRI) may provide additional insight into TSF risk and prognosis.

Body

In September 2003, the Principle Investigator status for this study was transferred to Dr. Peter Antich. This was in response to the departure of the original PI for a position in private practice. From this time until December 2004, significant review and revision of the study protocol was performed by both the local IRB and the Human Subjects Safety Review Board (HSSRB). In particular, the HSSRB was concerned that sedentary subjects would not be able to transition to training regime (30 minutes @ 6.0 mph/ 3 times weekly). The HSSRB approved a 1 month pre-training period to "ramp up" subjects to the prescribed exercise dose. In retrospect, this was entirely prescient of the future difficulties that we would encounter.

Recruitment of subjects was re-started in January 2005, with postings of flyers again on the campus of UT Southwestern Medical Center at Dallas. Subject recruitment showed us the existence of difficulties in recruiting a sufficient number of subjects satisfying the criteria agreed to from this University (both staff and students are very health- and exercise-conscious). In addition, the original protocol called for:

All subjects will not have ran for exercise for 1 year or more but will be within one standard deviation of the mean for the lean body mass appropriate for their height and weight.

In our experience, this condition did not have any bearing on whether a consented, sedentary subject would be able to perform the required training from the onset. In the end, significant efforts and resources were used in assessing and pre-training individuals. More than 50% of eligible subjects were not able to run at the required pace and would require pre-training. Eventually, the effort needed to support subjects in pre-training became unmanageable, so we choose to go ahead only with the fittest subjects and to potentially return to other consented, sedentary subjects in the future. We recognize that this may introduce some bias into our data. In similar future studies, a more rigorous fitness test should be included in the eligibility requirements to identify the subset of sedentary people who maintain good aerobic capacity. Thus, we also

observed that the typical individual who is able to run at 6.0 mph for 30 minutes and had not exercised in the previous year, meeting the sedentary criterion, was previously athletic.

To facilitate the MRI studies, a second consumer class treadmill (Pro-Form 350, Logan, UT) was purchased and temporarily housed at the Roger MRI Imaging Center in a room near the 1.5 T clinical imaging system. Subjects were directed to step off treadmill and jog with co-PI to MRI suite where they were positioned. A knee coil was used for all lower leg imaging, and mark was made with removable ink on the skin above the distal margin of the patella to reposition the coil after exercise. All measurements were made in the right leg.

A second difficulty was encountered, related to the MRI assessment of muscle recruitment. From the protocol:

***MRI/exercise testing:** After a scout sequence, a T2-weighted conventional spin echo sequence will be performed on the resting legs using a 1.5 T GE echo speed MRI device running on 8.3 version software. Sequence parameters are: TR = 2000 ms, TE = 30,100 ms; matrix 256 x 256, FOV 30 x 30, 1 NEX, 10 mm slice thickness with 5 mm gap. This provides 17 slices, spanning 23 cm of length of the leg. Centering will be at the mid-tibia. Following acquisition of the scan, the subject will be moved to the treadmill housed in the room next to the magnet where a 5 minute bout of running will proceed. Rate will be fixed at 10 minute/mile using a Trotter 535 device. Subjects assigned to the inclined running regimen will have 5 degrees inclination selected on the instrument. Immediately following exercise, the subject will be rescanned with a delay between exercise cessation and scanning of less than 90 seconds. Each test will require 30 minutes of scanner time.*

In practice, a 5 minute bout of exercise at low aerobic levels (6.0 mph) was not sufficient to differentiate pre-vs. post exercise MRI signals from the muscle groups in the lower leg. This was identified in a preliminary data analysis performed for the first four subjects in August 2006. Subsequent subjects completed an entire 30 minute training session between the MRIs. This data is currently being analyzed, but we suspect from the statement in the original protocol by the original PI, an MRI expert (*This experience is what dictates that the running protocol prior to MRI be quite vigorous*), that the exercise load must be much greater than the training regime in order to see muscle group recruitment on MRI. A significant anaerobic component may also be required. Future studies in this area will need to address this problem. As planned, each MRI imaging session was less than 30 minutes (approximately 20 minutes).

The initial data analysis of the UCR data also indicated that there was significant noise in the raw data for the 3rd generation ultrasound device used to assess tibial elasticity. This was caused by moving the device to a location near the training facilities, and it was rectified by complete disassembly and reassembly with new grounding straps for the electronics. Although baseline data was corrupted for the 1st four subjects, the subjects have kindly volunteered to return at a later time point (6 months to 1 year) to collect an additional data point to evaluate detraining or maintenance effects.

In 2005, we identified a subject exercising under the supervision of one of the co-Investigators (PS) as a prototypical forefoot runner. We have obtained a video showing

well-defined forefoot-running without coaching and have developed a short training video for subjects assigned to that research arm.

To summarize our experience with subjects under this protocol, a review of all consented subjects follows:

1. 25 year old Caucasian female, initial fitness 6.0 mph/30 minutes, completed protocol January 2007.
2. 26 year old Asian male, initial fitness 6.0 mph/30 minutes, completed protocol January 2007.
3. 31 year old Caucasian male, initial fitness 5.2 mph/15 minutes, subject assigned to pretraining regime w/ Dr. Snell, withdrew after 2 weeks complaining of knee-pain during exercise.
4. 26 year old Hispanic male, initial fitness 6.0 mph/30 minutes, completed protocol September 2006, available for detraining/maintenance UCR measurements.
5. 33 year old Hispanic male, initial fitness 5.8 mph/30 minutes, dropped out of study after 4 weeks training due to personal time constraints.
6. Asian female, initial fitness 6.0 mph/30 minutes, consented but no reply to further contact (training partner for subject #7)
7. Asian male, initial fitness 6.0 mph/ 30 minutes, consented but no reply to email contacts after baseline MRIs.
8. 24 year old Caucasian male, initial fitness 6.0 mph/ 30 minutes, completed protocol October 2006.
9. 25 year old Caucasian male, initial fitness 6.0/30 minutes, completed protocol October 2006.
10. Asian female, initial fitness 5.4 mph/30 minutes, had a car accident, withdrew after consent due to concerns regarding neck injury.
11. Caucasian male, initial fitness 6.0 mph/ 30 minutes, time constraints due to work and travel schedule of training partner (#17.) delayed start indefinitely.
12. Hispanic female, initial fitness 5.7 mph/30 minutes, job-related travel delayed start.
13. 24 year old Asian female, initial fitness 5.7/ 30 minutes, completed protocol in January 2007.
14. 29 year old Caucasian male, initial fitness 6.0/30 minutes, lost contact after consent.
15. Asian female, initial fitness 5.6 mph/30 minutes, non-compliant to running protocol during MRI baseline, withdrew from study.

16. 32 year old Caucasian female, initial fitness 5.2 mph/30 minutes, withdrew after consent on personal physician's recommendation.
17. Caucasian female, initial fitness 5.2 mph/15 minutes, assigned to pre-training, compliant subject increased to 5.8 mph/30 minutes in 6 weeks, withdrew before baseline assessment due to "lack of improvement."
18. C.B. Caucasian female, training partner for subj #19, consented but did not start study due to inconvenience of facilities.
19. Caucasian male, consented but time constraints of medical training delayed start repeatedly, lost contact.
20. Asian female, initial fitness 5.6 mph/30 minutes, completed protocol January 2007.
21. 25 year old Caucasian female, initial fitness 5.3 mph/20 minutes, assigned to pre-training, delayed pre-training to concentrate on fittest subjects.
22. 26 year old Caucasian female, initial fitness 5.2 mph/20 minutes, assigned to pre-training, delay to concentrate on fittest subjects.
23. 24 year old Caucasian male, initial fitness, 5.4 mph/30 minutes, assigned to pre-training, delayed to concentrate on fittest subjects.
24. 31 year old Caucasian female, initial fitness 5.0/10 minutes, smoker, assigned to pre-training, delayed to concentrate on fittest subjects, smoker.
25. 32 year old Caucasian female, initial fitness 5.2/10 minutes, assigned to pre-training, delayed to concentrate on fittest subjects, new child in previous year, will stop lactation before beginning.
26. 32 year old Middle Eastern female, initial fitness 4.0mph/30 minutes, assigned to pre-training, delayed, never been on treadmill, difficulty walking on belt.

In addition, four subjects consented in early 2005 were lost through lack of contact.

Key Research Accomplishments

- Training protocol completion for 8 subjects.
- Baseline data for 3 subjects who started but did not complete study.
- Development of training video for forefoot running.

Reportable Outcomes

Analysis is in progress and no directly reportable outcomes are available at this time. Although the initial protocol called for 40 subjects for sufficient statistical power, we will analyze the limited data in hand to ascertain any measurable changes. We anticipate presenting these results in poster form at a future conference. Although neither directly nor indirectly supported by this grant, one paper based on data collected with the third generation clinical UCR device used in this study has been published [3].

Conclusions

In retrospect, this study was ambitious in its goal of studying muscle-related changes in bone elasticity using training of sedentary individuals. We encountered many difficulties in maintaining subject compliance to the original study protocol. Although the protocol was clear in eligibility requirements for sedentary but otherwise healthy, young individuals, we observed that the majority of consented subjects could not run at the prescribed 6.0 mph for 30 minutes. For future studies in this area, it would be advantageous to further screen individuals to avoid the difficulties of pre-training subjects up to the required exercise load. In our experience, we expended great effort in assessing and training subjects who in the end could not provide data for this study. Future research efforts should focus more on acquiring larger imaging data sets rather than managing the exercise training program. Another option would be to perform similar studies in new military recruits, where motivation and fitness may be higher.

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